LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bactrim
(trimethoprim, sulfamethoxazole)

SE/H/1914/01/MR
1970-0157

This module reflects the scientific discussion for the approval of Bactrim. The procedure was finalised on 2020-10-21. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Roche AB has applied for a marketing authorisation for Bactrim, 40 mg/ml + 8 mg/ml, oral suspension. The active substance is trimethoprim and sulfamethoxazole (antibacterials for systemic use; sulfamethoxazole is a sulfonamide that competitively inhibits bacterial folic acid synthesis. Trimethoprim is a pyrimidine derivative and specifically inhibits dihydrofolic acid reductase in the micro-organisms. The combination of sulfonamide+trimethoprim blocks two consecutive steps in folic acid metabolism and thereby interrupts the synthesis of purine, RNA and DNA by the micro-organisms).

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The toxicological parts of the non-clinical information provided are in general based on a set of old toxicity studies conducted to support clinical trials and marketing authorization in the late 1960s and 1970s. Many of these data are superseded by data from clinical trials and experience in human. Given

the extensive and long clinical experience of more than 40 years, the safety of Bactrim could in applicable parts be based upon clinical data and experience. The lack of defined NOAELs and calculated margins to clinical exposure are therefore not critical. Furthermore, it is not considered relevant to add any information from the old animal studies or the non-verified non-clinical data to the SmPC.

III.2 Pharmacology

For mode of action and primary pharmacology, see the Clinical aspects below.

No specific information on secondary pharmacological effects or safety pharmacological parameters of sulfamethoxazole and trimethoprim are available. Considering the clinical experience with the compounds this is considered acceptable.

III.3 Pharmacokinetics

No information on pharmacokinetics (PK) in animals is provided. This is acceptable considering the well-known non-clinical toxicological profiles of sulfamethoxazole and trimethoprim alone and in combination together with the long clinical experience and knowledge of the clinical pharmacokinetics of the compounds following oral treatment with Bactrim.

III.4 Toxicology

General toxicity
Data from old repeated dose toxicity studies of Bactrim (i.e. following intravenous administration for 4 weeks to rats, dogs and monkeys and following orally administered trimethoprim and sulfamethoxazole, singly or in a 1:5 combination, for 60 and 52 weeks to monkeys and rats, respectively) were provided. The GLP-compliance of the studies are not known.

One of the findings in rats and dogs consisted of increased absolute and relative thyroid weights accompanied by a dose-related hyperplasia which were observed from the lowest IV dose of 8 mg trimethoprim/kg + 40 mg sulfamethoxazole/kg in dogs and from the middle IV dose of 16 mg trimethoprim/kg + 80 mg sulfamethoxazole/kg in rats. In the 60-week oral study in rats, thyroid hyperplasia of a dose-related severity was seen after 13 weeks in all animals, i.e. from a sulfamethoxazole dose level of 25 mg sulfamethoxazole/kg, which progressed to nodularity or adenoma formation in some rats after 52 weeks at sulfamethoxazole doses of 50 mg/kg per day. This a known finding of sulfonamides and anti-thyroid drugs in rats and has been explained by an excessive and prolonged stimulation of the thyroid epithelium by the thyrotropic secretion of the pituitary induced by the compounds indirectly.

Other histopathological effects associated with sulfamethoxazole include dose-related testicular atrophy, focal renal calcification, and slightly increased fat vacuolation of the liver and kidney.

Otherwise the findings consisted of effects which can be monitored in the clinic (e.g. dose-related decreases in some hematology parameters in dogs and monkeys, increases in some blood-chemistry parameters such as alkaline phosphatase and cholesterol in dogs and changes in ECG parameters such as arrythmias, prolongation of the PQ interval and intermittent AV-blocks in dogs) or are not relevant for oral administration.

Genotoxicity
Whereas trimethoprim is reported to be non-mutagenic in an Ames test stated to be GLP-compliant there is no information on the effect of sulfamethoxazole in a bacterial reverse mutation test. Due to the low concentrations that could be tested in the Ames test of trimethoprim these results are however of limited value. The information from *in vitro* and *in vivo* studies on chromosomal effects of sulfamethoxazole and trimethoprim alone or in combination in human leucocytes presented in the non-clinical overview are not verified by references and there is no information from *in vivo* animal studies on micronuclei or chromosomal damage. Thus, the information available do not meet the current

requirement for a standard test battery for genotoxicity. The genotoxic potential of sulfamethoxazole and trimethoprim are therefore not considered to be fully evaluated. No signals of genotoxic or carcinogenic effects are however reported during the time period when Bactrim has been authorized.

Carcinogenicity
Due to the short treatment period for Bactrim (in general no longer than 7 days except for patients with renal impairment which can be treated as long as follow-up tests permit) and no indication of a genotoxic potential of sulfamethoxazole and trimethoprim, data from studies of carcinogenic effects in animals are not required.

Reproductive and developmental toxicity
A study of effects on fertility and general reproduction did not reveal any treatment related effects on fertility and general reproduction following oral treatment of trimethoprim and sulfamethoxazole in combination up to doses of 70 mg/kg/day and 350 mg/kg/day, respectively.

In a study of effects on embryofetal development in rats, small and underdeveloped kidneys were noted with a low but a slightly higher incidence at the highest combined oral dose of 70 mg/kg/day trimethoprim and 350 mg/kg/day sulfamethoxazole than in the other treatment groups. No dose-related differences were reported for skeletal anomalies or litter data. In rabbits, little or no differences were noted between the treated groups and the control group with regards to general reproduction performance. There were no increases in external, visceral and/or skeletal abnormalities after treatment with oral doses up to 70 mg/kg/day trimethoprim and 350 mg/kg/day sulfamethoxazole as compared to vehicle.

Non-verifiable information of teratogenic effects in rats, mainly manifested as cleft palates, following doses of sulfamethoxazole alone and in combination with trimethoprim that were higher or comparable to those in the submitted study was also provided. The lowest dosage at which teratogenic effects were reported was 355 mg/kg sulfamethoxazole in combination with 88 mg/kg trimethoprim, when cleft palates were observed in one litter out of 9.

In SmPC section 4.6 it is stated that trimethoprim and sulfamethoxazole may interfere with folic acid metabolism and that animal experiments have shown that very high doses of trimethoprim and sulfamethoxazole given during organogenesis produce fetal malformations typical of folic acid antagonism. Due to the long clinical experience of treatment with Bactrim including outcome of a large numbers of exposed pregnancies together with the recommendations in SmPC section 4.6 (to avoid treatment during pregnancy and to give pregnant women or women planning to become pregnant daily doses of folic acid in case treatment with Bactrim is considered necessary), animal data on effects on embryonal development can be considered as superseded.

Studies of peri- postnatal development of oral doses up to 70 mg/kg/day trimethoprim and 350 mg/kg/day sulfamethoxazole in combination did not induce any dose-related effects on gestation or in offspring of treated rats. Based on to the knowledge of the excretion of trimethoprim and sulfamethoxazole into breast milk and the recommendations regarding breast-feeding in SmPC section 4.6, animal data on peri- and postnatal development can be considered as superseded.

III.5 Ecotoxicity/environmental risk assessment (ERA)

There is insufficient data for a conclusion on the environmental risk. The Applicant has committed to provide a full updated ERA and corresponding section of the non-clinical overview by the end of January 2023. Assessment of the environmental risk of Bactrim will be performed when the updated ERA is received.

III.6 Discussion on the non-clinical aspects

Except for the ERA, the provided non-clinical information provided are considered acceptable in support of the safety profile of sulfamethoxazole + trimethoprim used in accordance with the SmPC. A full updated ERA will be received by the end of January 2023.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application consists of data for a well-established product consisting of the combination of sulfamethoxazole (SMZ) + trimethoprim (TMP), which has been authorised in Sweden for more than 45 years.

Bactrim contains two active substances, sulfamethoxazole (SMZ) and trimethoprim (TMP), and is used as an antibacterial for systemic use. One mL of oral solution contains sulfamethoxazole 40 mg and trimethoprim 8 mg.

The approved indications in Sweden for Bactrim 40 mg/mL+ 8 mg/mL oral solution are the following:

- Bactrim oral solution is indicated for adults, adolescents, children and neonates from the age of 6 weeks in the following indications:
  Upper urinary tract infections. Complicated lower urinary tract infections. Prostatitis. Serious infections originating from the urinary tract. Acute exacerbation of chronic bronchitis. Shigellosis. Typhoid and paratyphoid fever. Prophylaxis and treatment of infections caused by *Pneumocystis jirovecii*, particularly in severely immunocompromised patients.

- Consideration should be given to official guidance on the appropriate use of antibacterial agents and the local resistance situation.

The approved posology is:

> Treatment should be continued until the patient has been symptom-free for 2 days and should normally not exceed 7 days. In fulminant infections the dose can be increased by 50% in all age groups. Oral solution should be shaken before use.
>
> *Adults and children over 12 years of age:* 20 mL Bactrim oral solution morning and evening.
> *Children from 6 years to 12 years of age:* 10 mL Bactrim oral solution morning and evening.
> *Children from 6 months to 5 years of age:* 5 mL Bactrim oral solution morning and evening.
> *Children from 6 weeks up to 5 months of age:* 2.5 mL Bactrim oral solution morning and evening.
>
> The dosage for children is equivalent to a dose of approximately 6 mg trimethoprim and 30 mg sulfamethoxazole per kg body weight per day.
>
> Further details are outlined in the SmPC, in section 4.2.

IV.2 Pharmacokinetics

Absorption

SMZ + TMP are rapidly and completely absorbed from the upper portion of the gastrointestinal tract after oral administration, the absolute oral bioavailability reaching 100% for both drugs. The peak serum concentration of Bactrim is reached within 2–4 hours after oral administration. The serum concentrations of the respective substances on repeated administration are 6.5 (5.2–10.3) micromol/L =1.9 (1.5–3.0) micrograms/mL (trimethoprim), 225 (150–300) micromol/L =56 (37.5–75) micrograms/mL (sulfamethoxazole).

Distribution

The volume of distribution is about 1.6 l/kg for trimethoprim and about 0.2 l/kg for sulfamethoxazole. Plasma protein binding is up to 37% for trimethoprim and 62% for sulfamethoxazole. In humans, trimethoprim and sulfamethoxazole are detected in foetal tissue (placenta, liver, lung), umbilical cord blood and amniotic fluid, indicating that both substances cross the placenta. Both substances are excreted in breast milk. The concentrations in breast milk are generally similar to plasma concentrations in the mother for trimethoprim and slightly lower for sulfamethoxazole.

Metabolism

About 30% of the trimethoprim dose is metabolised. Results from an in-vitro study with human liver microsomes show that CYP3A4, CYP1A2 and CYP2C9 are predominantly responsible for the metabolism of trimethoprim. The main metabolites of trimethoprim are 1 and 3-oxides and 3- and 4-hydroxy derivatives; certain metabolites are microbiologically active.
About 80% of the sulfamethoxazole dose is metabolised in the liver, preferentially to the N4 acetyl derivative (≈ 40% of the dose), and to a lesser extent by glucuronide conjugation. Sulfamethoxazole also undergoes oxidative metabolism. The first step in oxidative metabolism, which results in the formation of the hydroxylamine derivative, is catalysed by CYP2C9.

Elimination

The half-life of the two components is the same (a mean of 10 hours for trimethoprim and 11 hours for sulfamethoxazole).
Trimethoprim and sulfamethoxazole are eliminated via the kidneys by glomerular filtration; trimethoprim is also eliminated by tubular secretion. Sulfamethoxazole is 20% eliminated as unchanged active substance. Approximately two thirds of trimethoprim is excreted unchanged in the active form. Total plasma clearance of trimethoprim is 1.9 mL/min/kg and for sulfamethoxazole 0.32 mL/min/kg. A small proportion of each substance is eliminated via the faeces.

Paediatric population

The pharmacokinetics for both components of Bactrim, trimethoprim and sulfamethoxazole, are age-dependent in the paediatric population with normal renal function.

Patients with impaired renal function

In patients with severely impaired renal function (creatinine clearance 15-30 mL/min), the half-life of both substances is prolonged, necessitating a dose adjustment.

Patients with impaired hepatic function

The pharmacokinetics of trimethoprim and sulfamethoxazole in patients with moderately or severely impaired hepatic function is thought not to be significantly different from that observed in healthy subjects.

Interactions

Trimethoprim is an inhibitor of the organic cation transporter 2 (OCT2), the MATE1/2-K transporters and is a weak inhibitor of CYP2C8. Sulfamethoxazole is a weak inhibitor of CYP2C9. Thus, the exposure of medicinal products predominantly metabolised by CYP2C8 or CYP2C9 and medicinal products transported by OCT2, MATE1 and MATE2-K may be affected by coadministration with Bactrim.
Further, the product contains the excipient sorbitol which potentially can affect the bioavailability of other co-administrated products. This is reflected in section 4.4 of the SmPC which is appropriate for an excipient. There is no indication that sorbitol affects the bioavailability of either TMP or SMZ.

IV.3 Pharmacodynamics

Mechanism of action

Bactrim is a combination of two antimicrobial agents, trimethoprim (TMP) and sulfamethoxazole (SMZ), in a 1:5 ratio. Both agents inhibit bacterial synthesis of tetrahydrofolic acid, the physiologically active form of folic acid and a necessary cofactor in the synthesis of thymidine, purines, and bacterial DNA. Sulfamethoxazole inhibits synthesis of the intermediary dihydrofolic acid from its precursors. Trimethoprim competitively inhibits dihydrofolate reductase (DHFR). This sequential blockade of two enzymes in one pathway results in an effective bactericidal action. This mechanism usually results in bactericidal activity in vitro at concentrations at which the individual substances are only bacteriostatic. In addition, Bactrim is often effective against organisms that are resistant to one of the two components.

Primary pharmacology – Spectrum of activity

Bactrim possesses broad-spectrum antibacterial activity, and is also active against some non-bacterial microbes, particularly the fungus *Pneumocystis jirovecii* (formerly *P. carinii)* and the parasite *Toxoplasma gondii.* The European Committee on Antimicrobial Susceptibility Testing (EUCAST) have published MIC breakpoints for SMZ + TMP against bacterial taxa.

The pharmacodynamic effects

The pharmacodynamic effects of SMZ + TMP are well established. The data provided by the MAH adequately covers the pharmacodynamic aspects.

IV.4 Clinical efficacy

Bactrim, SMZ + TMP, was authorized in Sweden 20th of October 1972 and is indicated for treatment of upper urinary tract infections, complicated lower urinary tract infections, prostatitis, serious infections originating from the urinary tract, shigellosis, typhoid-and paratyphoid fever, acute exacerbation of chronic bronchitis and treatment and prevention of *Pneumocystis jiroveci* pneumonitis. Extrapolation from adult data during the development of the product resulted in the inclusion of the paediatric population in the label. It is important to be aware of the large national/regional variations in SMZ+TMP resistance in order to choose a proper antibiotic. Before prescribing an antibiotic, including Bactrim, national/local guidelines on the use of antibiotics should always be considered. Bactrim is approved from 6 weeks of age in most countries.

In support of the current application Bactrim 40 mg/mL+ 8 mg/mL oral solution the MAH has submitted data from five MAH sponsored clinical studies using oral suspension in the relevant indications, and recent relevant bibliographic clinical data. None of the studies for the original approval in 1972 has been provided by the MAH, which is considered reasonable when taking into account that the approval of this product was a 45 years ago. All conditions treated in the submitted studies are among the already approved indications in the SmPCs. Overall, the results from the Roche supported studies are acceptable and present a high percent of positive clinical outcome after treatment with SMZ+TMP. Consequently, the results of the submitted studies support the indications already listed in the SmPCs.

The use of SMZ+TMP to treat *Pneumocystis jirovecii* pneumonia in both children and adults is well described in the literature and the indication is considered sufficiently justified. The combination of SMZ + TMP is well characterized for treatment of LRTI where susceptible agents is associated with the disease, the treatment is used both in both children and adults. The efficacy rate for using SMZ+TMP for treatment of LRTI appears to be within similar range as for treatment with amoxicillin or ciprofloxacin. Sufficient data has been provided to support that the combination of SMZ+TMP is a treatment option for infections related to the urinary tract. The provided literature data supports the indication that the combination of SMZ+TMP can be used to treat shigellosis. Treatment of

Salmonella typhimurium and the use of SMZ+TMP as a treatment option for prostatitis was described in the initial documentation provided by MAH for the national application in 1972 and those indications have remained unchanged since then. The indications typhoid/paratyphoid fever and prostatitis are considered acceptable. Thus, the literature data support the use of SMZ+TMP in the approved indication.

IV.5 Clinical safety

The safety profile of SMZ+TMP is considered well-established since the product has been approved and used in clinical practice for over 45 years. The total estimated cumulative market exposure to SMZ + TMP during the period 1 January 1974 to 31 March 2018 was 2,041,477,307 patients (1,196,728,077 adult use; 844,749,230 paediatric use) based on Roche Pharma only which provides a robust post marketing safety database.

Common adverse events associated with the clinical use of SMZ+TMP are rash, pyrexia, pruritus, urticaria, thrombocytopenia. In the previous PSUR the review of the PSUR interval data did not identify any new safety concerns or a change in a reporting pattern with regard to frequency and/or severity, which could impact the well-known safety profile of SMZ + TMP.

The incidence of AEs in the MAH sponsored paediatric clinical studies was rather similar for SMZ+TMP and the reference treatment groups. The safety data from the studies submitted did not raise any concern of new safety signals.

The risks associated with the use of SMZ+TMP are well defined and are properly covered in the Contraindications, Special warnings and precautions for use and Interactions with other medicinal products and other forms of interactions sections of the SmPC.

IV.6 Risk Management Plans

The MAH has submitted a risk management plan, version 1.0, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Bactrim.

Safety specification

The MAH has provided a Risk Management Plan, version 1.0 where the following summary of safety concerns in the RMP was proposed. This update of the RMP was assessed in a recent type II variation, 5.4.3-2019-10403.

Table Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None.

In line with the GVP module V (rev 2), the MAH has deleted “kernicterus in neonates”, “drug-drug interaction with dofetilide with potential to cause cardiac arrhythmias”, “drug reaction with eosinophilia and systemic symptoms (DRESS)”, “Stevens Johnson syndrome (SJS) / Toxic epidermal necrolysis (TEN)”, “fulminant liver necrosis” and also “blood dyscrasias” since neither of the safety concerns is associated with additional pharmacovigilance or risk-minimisation activities. In addition, it is considered by the RMS that the SmPC covers relevant and adequate the information, and thus, the proposed summary of safety concerns is acceptable.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the MAH, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the MAH, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version 1.0 signed is considered acceptable.

IV.7 Discussion on the clinical aspects

Overall, the clinical pharmacokinetics, pharmacodynamics, clinical efficacy and safety profile of SMZ+TMP for use in the relevant indications are well established and supported by the data submitted by the MAH.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The user test was assessed and accepted with the national variation no. (dnr): 5.4.3-2019-10403.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The combination of the two well-known active substances, sulfamethoxazole (SMZ) and trimethoprim (TMP), has been used all over the world for many decades as a systemic antibacterial.

The SMZ+TMP combination possesses broad-spectrum antibacterial activity, and is also active against some non-bacterial microbes, particularly the fungus *Pneumocystis jirovec*i (formerly P. carinii) and the parasite Toxoplasma gondii.

In Sweden SMZ+TM as Bactrim has been approved since October 20th, 1972. Bactrim oral solution is indicated for adults, adolescents, children and neonates from the age of 6 weeks in the following indications:

- Upper urinary tract infections.
- Complicated lower urinary tract infections.
- Prostatitis.
- Serious infections originating from the urinary tract.
- Acute exacerbation of chronic bronchitis.
- Shigellosis.
- Typhoid and paratyphoid fever.
- Prophylaxis and treatment of infections caused by *Pneumocystis jirovec*i, particularly in severely immunocompromised patients.

In support of the current application Bactrim 40 mg/mL+ 8 mg/mL oral solution the MAH has submitted data from a limited number of MAH sponsored clinical studies and recent relevant bibliographic clinical data. Overall, the MAH has provided sufficient documentation to support the approved indications in children, adolescents and adults.

The safety profile of SMZ+TMP is considered well-established since the product has been approved and used in clinical practice for over 45 years. The total estimated cumulative market exposure to SMZ + TMP during the period 1 January 1974 to 31 March 2018 was 2,041,477,307 patients (1,196,728,077 adult use; 844,749,230 paediatric use) based on Roche Pharma only which provides a robust post marketing safety database. The risks associated with the use of SMZ+TMP are well defined and are properly covered in the Contraindications, Special warnings and precautions for use and Interactions with other medicinal products and other forms of interactions sections of the SmPC.

The benefit/risk ratio is considered positive and Bactrim, 40 mg/ml + 8 mg/ml, oral suspension is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The mutual recognition procedure for Bactrim, 40 mg/ml + 8 mg/ml, oral suspension was positively finalised on 2020-10-21.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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